Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: Protease Inhibitors (PIs)

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Atazanavir (ATV)**	**Fosamprenavir (f-APV)**
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities.	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities. Dose: Dose adjustment for patients receiving > 400 mg/day may be needed.
Ketoconazole	Unboosted: No dosage adjustment necessary. RTV boosted: See RTV recommendations.	No data, but presumably similar interaction as seen with APV with an increase in both APV and ketoconazole levels (APV ↑ 31%; ketoconazole ↑ 44%). Dose: Consider ketoconazole dose reduction if dose is > 400 mg/day. If f-APV/r: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	RTV boosted: No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities. See RTV recommendations if boosted with RTV.	No data, but potential for bi-directional inhibition between voriconazole and PIs; monitor for toxicities. See RTV recommendations if boosted with RTV.
ANTI-MYCOBACTERIALS		
Clarithromycin	Levels: clarithromycin AUC ↑ 94% and may cause QTc prolongation. Clarithromycin active metabolite concentrations are significantly reduced. Dose: ↓ clarithromycin dose by 50%. Consider alternative therapy.	Presumably similar interaction and recommendation as APV. Levels: APV AUC ↑ 18%. No change in clarithromycin AUC. No dose adjustment.
Rifabutin	Levels: Rifabutin AUC ↑ 2.5-fold Dose: ↓ rifabutin dose to 150 mg QOD or 3x/week[¢]	Rifabutin 150 mg QOD + fAPV 700/100 mg BID, rifabutin unchanged. No data on f-APV level. Dose: No change in f-APV dose; decrease rifabutin to 150 mg QD or 300 mg 3x/week[¢]. If RTV-boosted f-APV, reduce rifabutin dose to 150 mg QOD or 3x/week[¢].
Rifampin	Should not be coadministered.	A substantial decrease in APV AUC (≈ ↓ 82%) is expected based on the interaction with APV. Should not be co-administered.
HORMONAL CONTRACEPTIVES		
	Levels: Ethinyl estradiol AUC ↑ 48%, norethindrone AUC ↑ 110% Dose: use lowest effective dose or alternative methods.	An increase in ethinyl estradiol and norethindrone levels occurred with APV, and APV levels ↓ 20%. Do not co-administer; alternative methods of contraception are recommended.
LIPID–LOWERING AGENTS		
Atorvastatin	Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 150% - use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease ATV levels substantially. Monitor anticonvulsant level and virologic response. Consider using alternative anticonvulsant or monitoring ATV level and boosting with RTV if necessary.	Unknown, but may decrease APV levels substantially. Monitor anticonvulsant levels and virologic response, or consider alternative anticonvulsant. Consider monitoring APV levels and boosting with RTV if necessary.
METHADONE	No change in methadone or ATV levels.	With APV, R-methadone levels ↓ 13%, and APV Cmin ↓ 25%. The interaction with f-APV is presumed to be similar. Monitor and titrate methadone if needed.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil levels have potential for increase. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2- to 11-fold with APV. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	No data, but concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.
MISCELLANEOUS	Diltiazem: AUC ↑ 125%, ↓ diltiazem dose by 50%; ECG monitoring is recommended. Other calcium channel blockers: caution is warranted; dose titration should be considered; ECG monitoring is recommended. Irinotecan: ATV inhibits UGT and may interfere with irinotecan metabolism; avoid concomitant use. H2-receptor antagonists: reduced ATV concentrations with simultaneous administration; in treatment-naïve, give ATV at least 10 hrs after or 2 hrs before H2-receptor antagonist, or use ATV/r 300/100 mg; in treatment-experienced, boost ATV and administer separately. Proton-Pump Inhibitors: Co-administration with these agents may significantly decrease ATV solubility. Do not co-administer. Antacids and buffered medications: Reduced ATV concentrations are expected with simultaneous administration; give ATV 2 hrs before or 1 hr after these medications.	H2 Blockers: Co-administration of ranitidine with f-APV decreases (↓) APV AUC 30%; Cmin unchanged. Separate administration if co-administration is necessary. Monitor closely for desired virologic response. Consider boosting with RTV. Proton-Pump Inhibitors: No effect of esomeprazole 20 mg on APV AUC, C_{max}, or C_{min}, regardless of whether f-APV was given with or without ritonavir.

[¢] Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Indinavir (IDV)**	**Lopinavir + Ritonavir (LPV/r)**
ANTIFUNGALS		
Itraconazole	Level: When IDV 600 mg Q8H given with itraconazole 200 mg bid, IDV AUC similar to IDV 800 mg Q8H. Dose: IDV 600 mg Q8H; Itraconazole: Do not exceed 200 mg BID.	Levels: Itraconazole ↑ when administered with LPV/r. Dose: Itraconazole – consider not exceeding 200 mg/day, or monitor level and toxicity.
Ketoconazole	Levels: IDV ↑ 68%. Dose: IDV 600 mg Q8H.	Levels: LPV AUC ↓ 13%. Azole ↑ 3-fold. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	Levels: No significant changes in AUC of azole or IDV (healthy subjects). See RTV recommendations if boosted with RTV. Dose: Standard	Voriconazole AUC ↓ 39% with RTV 100 mg BID; Co-administration is not recommended unless the benefit outweighs the risk.
ANTI-MYCOBACTERIALS		
Clarithromycin	Levels: Clarithromycin ↑ 53%. No dose adjustment.	Levels: ↑ Clarithromycin AUC 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
Rifabutin	Levels: IDV ↓ 32%. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150 mg per day or 300 mg 3x/week.[¢] IDV 1,000 mg Q8H. If RTV boosted, rifabutin 150mg QOD or 3x/week[¢] continue current dose of boosted IDV.	Levels: Rifabutin AUC ↑ 3-fold. 25-O-desacetyl metabolite ↑ 47.5-fold. Dose: Decrease rifabutin dose to 150 mg QOD or 3x/week[¢]; LPV/r: Standard.
Rifampin	Levels: IDV (unboosted) ↓ 89%; IDV (boosted) ↓ 87%; **Should not be coadministered.**	Levels: LPV AUC ↓ 75%.* **Should not be coadministered.**
HORMONAL CONTRACEPTIVES		
	Levels: Norethindrone ↑ 26%. Ethinylestradiol ↑ 24%. No dose adjustment.	Levels: ethinyl estradiol ↓ 42%. Use alternative or additional method.
LIPID–LOWERING AGENTS		
Atorvastatin	Levels: Potential for increase in atorvastatin levels. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 5.88-fold. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No Data.	Pravastatin AUC ↑ 33%; no dosage adjustment necessary.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Carbamazepine markedly ↓ IDV AUC. Consider alternative anticonvulsant, ritonavir-boosting, and/or monitoring IDV level.	Many possible interactions: carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓ levels of LPV, RTV, and ↓ levels of phenytoin when administered together. Avoid concomitant use or monitor LPV level.
METHADONE	No change in methadone levels.	Methadone AUC ↓ 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil AUC ↑ 3-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11-fold in combination with RTV. Do not exceed 25 mg every 48 hours.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil AUC ↑ 124% when co-administered with RTV. Do not exceed a single dose of 10 mg every 72 hours.
Vardenafil	Vardenafil AUC ↑ 16-fold. IDV (unboosted) AUC ↓ 30%. Dose: Consider sildenafil instead of vardenafil if IDV unboosted. Do not exceed vardenafil 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Do not exceed a single 2.5 mg dose in 72 hours.
MISCELLANEOUS	Grapefruit juice ↓ IDV levels by 26%. Vitamin C ≥1 gram/day ↓ IDV AUC by 14% and Cmin by 32%. Amlodipine: Amlodipine AUC ↑ 90% when co-administered with IDV/RTV. No change in IDV/RTV levels. Monitor closely.	LPV/r levels unchanged when tablets are given with omeprazole or ranitidine.

[¢] Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3.

* In one small study, higher doses of RTV (an additional 300 mg BID) or a double dose of LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued treatment because of increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Nelfinavir (NFV)**	**Ritonavir* (RTV)**
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs; monitor for toxicities.	No data, but potential for bi-directional inhibition between itraconazole and RTV; monitor for toxicities. Dose: Dose adjustment for patients receiving > 400 mg itraconazole may be needed, or consider monitoring itraconazole level.
Ketoconazole	No dose adjustment necessary.	Levels: ketoconazole ↑ 3X. Dose: Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities.	Levels: voriconazole AUC ↓ 82% when co-administered with 400 mg BID of RTV, and concomitant therapy of voriconazole with RTV 400 mg BID or higher is contraindicated. Voriconazole AUC ↓ 39% with RTV 100 mg BID; administration of voriconazole and RTV 100 mg is not recommended unless benefit outweighs risk.
ANTI-MYCOBACTERIALS		
Clarithromycin	No data.	Levels: Clarithromycin ↑ 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
Rifabutin	Levels: NFV ↓ 32% if 750 mg Q8H dose given; no change if 1,250 mg Q12H dose used. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150 mg QD or 300 mg 3x/wk.[¢] NFV 1,250 mg BID.	Levels: Rifabutin ↑ 4X. Dose: ↓ rifabutin to 150 mg QOD or dose 3x/week.[¢] RTV: Maintain current dose.
Rifampin	Levels: NFV ↓ 82%. **Should not be coadministered.**	Levels: RTV ↓ 35%. Increased liver toxicity possible. Co-administration may lead to loss of virologic response if RTV sole PI. Alternative antimycobacterial agents, such as rifabutin, should be considered. **Should not be coadministered.**
HORMONAL CONTRACEPTIVES		
	Levels: Norethindrone ↓ 18%. Ethinyl estradiol ↓ 47%. Use alternative or additional method.	Levels: Ethinyl estradiol ↓ 40%. Use alternative or additional method.
LIPID–LOWERING AGENTS		
Atorvastatin	Atorvastatin AUC ↑ 74%. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	Levels: 50% ↓ when administered with SQV/RTV combination. Dose: Pravastatin dosage adjustment based on lipid response.
Simvastatin **Lovastatin**	Simvastatin AUC ↑ 505%. Potential for large increase in lovastatin AUC. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virologic response. Consider alternative anticonvulsant or NFV levels.	Carbamazepine: ↑ serum levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels.
METHADONE	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil AUC ↑ 2- to 11-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours; monitor for adverse effects.	Sildenafil AUC ↑ 11-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	Tadalafil AUC ↑ 124%. Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49 fold. RTV AUC ↓ 20%. Dose: Vafdenafil: Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 72 hours. RTV: Maintain current dose.
MISCELLANEOUS		Many possible interactions. Desipramine ↑ 145%; reduce dose. Trazodone AUC ↑ 2.4-fold when given with RTV 200 mg BID. Use lowest dose of trazodone and monitor for CNS and CV adverse effects. Theophylline ↓ 47%; monitor theophylline levels. RTV 100 mg BID significantly increases systemic exposure of inhaled (oral or nasal) fluticasone and may predispose patients to systemic corticosteroid effects. Co-administration not recommended unless benefit of fluticasone outweighs the risk.

* Drugs for which plasma concentrations may be decreased by co-administration with ritonavir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

¢ Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3.

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Saquinavir[†] (SQV)**	**Tipranavir + Ritonavir (TPV/RTV)**
ANTIFUNGALS		
Itraconazole	Bi-directional interaction between itraconazole & SQV has been observed. Dose: Not established, but decreased itraconazole dosage may be warranted. Consider therapeutic drug monitoring for both SQV (if unboosted) and itraconazole.	No data. Use with caution; do not exceed 200 mg itraconazole daily.
Ketoconazole	Levels: SQV ↑ 3X. Dose: No dosage adjustment necessary.	No data. Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities	Potential for bi-directional inhibition between voriconazole and PIs exists. Voriconazole AUC ↓ 39% with RTV 100 mg BID; interaction between TPV and voriconazole unknown. Co-administration is not recommended unless the benefit outweighs the risk.
ANTI-MYCOBACTERIALS		
Clarithromycin	Levels: Clarithromycin ↑ 45%. SQV ↑ 177%. Dose: No dose adjustment.	Levels: TPV ↑ 66%, Clarithromycin ↑ 19%, 14-hydroxy-clarithromycin metabolite ↓ 97%. Dose: No adjustment for patients with normal renal function; reduce clarithromycin dose by 50% for CrCl 30-60 mL/min; reduce clarithromycin dose by 75% for CrCl <30 mL/min.
Rifampin	Levels: SQV ↓ 84%. Marked elevation of transaminases was seen in a pharmacokinetic study, where healthy volunteers received a combination of rifampin 600 mg QD + RTV/SQV 100/1,000 mg BID. This combination should not be used.	No data; should not be coadministered.
Rifabutin	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150 mg qod or 3x/week.[¢]	Levels: Rifabutin AUC ↑ 2.9-fold. 25-O-desacetyl metabolite ↑ 20.7-fold. Dose: Decrease rifabutin dose to 150 mg QOD or 3x/week.[¢] Single-dose study, thus the effect of multiple doses of rifabutin on TPV/r PK was not assessed.
HORMONAL CONTRACEPTIVES		
	No data.	Levels: Ethinyl estradiol Cmax and AUC ↓ ~ 50%.[a] Use alternative or additional method. Women on estrogen may have increased risk of non-serious rash. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.
LIPID–LOWERING AGENTS		
Atorvastatin	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: atorvastatin AUC ↑ 9-fold. Dose: Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. Dose: Pravastatin dosage adjustment based on lipid response.	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may markedly ↓ SQV levels. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider monitoring SQV level.	No data. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider obtaining TPV level.
METHADONE	Methadone AUC ↓ 20% when co-administered with SQV/RTV 400/400 mg BID. Dose: No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.	No data. Dosage of methadone may need to be increased when co-administered with TPV/r.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil AUC ↑ 2-fold. Use a 25 mg starting dose of sildenafil.	No data. Starting dose should not exceed 25 mg sildenafil within 48 hours.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mg dose, and do not exceed a single dose of 10 mg every 72 hours.	No data. Starting dose should not exceed 10 mg tadalafil every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed a single 2.5 mg dose in 72 hours if administered with RTV.	No data. Starting dose should not exceed 2.5 mg vardenafil every 72 hours.
MISCELLANEOUS	Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels.	Abacavir ↓ 35-44%.[a] Appropriate doses for the combination of ABC and TPV/r have not been established. Zidovudine ↓ 31-43%. Appropriate doses for the combination of ZDV and TPV/r have not been established. Loperamide ↓ 51%.[a] TPV Cmin ↓ 26% with loperamide. Antacids ↓ TPV ~30%, TPV should be administered 2 hrs before or 1 hr after these medications. Fluconazole: Doses > 200 mg/day are not recommended to be given with TPV. TPV capsules contain alcohol. Avoid use of disulfiram and metronidazole.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200 mg BID.

[†] Some drug interaction studies were conducted with Invirase® soft gel capsule. May not necessarily apply to use with Fortovase.

Table 21b. Drug Interactions Among Antiretrovirals and Other Drugs: NNRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Delavirdine (DLV)**	**Efavirenz (EFV)**	**Nevirapine (NVP)**
ANTIFUNGALS			
Fluconazole	No clinically significant changes in DLV or fluconazole concentrations.	No clinically significant changes in EFV or fluconazole concentrations.	Levels: NVP: Cmax, AUC, and Cmin ↑ 100%. Fluconazole: No change.Risk of hepatotoxicity may ↑ with this combination. If co-administered, monitor NVP toxicity.
Ketoconazole	DLV: Cmin ↑ 50%. Ketoconazole: No data. Dose: Standard.	No data.	Levels: Keto ↓ 63%. NVP ↑ 15%-30%. Dose: Not recommended.
Voriconazole	Metabolism of voriconazole may be inhibited by DLV. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Levels: EFV ↑ 44%. Voriconazole ↓ 77%. This combination is not recommended.	Metabolism of voriconazole may be induced by NVP. Voriconazole may inhibit NNRTI metabolism. Carefully monitor for NNRTI toxicity and antifungal outcome.
ANTI-MYCOBACTERIALS			
Clarithromycin	Levels: Clarithromycin ↑ 100%. DLV ↑ 44%. Adjust dosage for renal failure.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.	Levels: NVP ↑ 26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent
Rifabutin	Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended.	Levels: EFV unchanged. Rif ↓ 35%. Dose: ↑ rifabutin dose to 450-600 mg QD or 600 mg 3x/week.* EFV: Standard.	Levels: NVP ↓ 16%. No dose adjustment.*
Rifampin	Levels: DLV ↓ 96%. Contraindicated.	Levels: EFV ↓ 25%. Dose: Maintain EFV dose at 600mg QD in patients weighing <50 kg or consider ↑ EFV to 800 mg QD.	Levels: NVP ↓ 20%-58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. Combination is not recommended; if used, co-administration should be done with careful monitoring.
HORMONAL CONTRACEPTIVES			
	Levels of ethinyl estradiol may increase. Clinical significance is unknown.	Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods.	Levels: Ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.
LIPID–LOWERING AGENTS			
Atorvastatin	Potential for inhibition of atorvastatin metabolism. Use lowest possible dose and monitor for toxicity.	Levels: Atorvastatin AUC ↓43%; EFV unchanged. Dose: Adjust atorvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	No data.
Pravastatin	No data.	No data.	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Simvastatin AUC ↓ by 58%; EFV unchanged. Dose: Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	No data.
ANTICONVULSANTS			
Carbamazepine **Phenobarbital** **Phenytoin**	Levels: DLV Cmin ↓ 90% when co-administered with phenytoin, phenobarbital, or carbamazepine. Contraindicated.	Use with caution. CBZ and EFV AUCs ↓ 27% and 36%, respectively, when combined. One case report showed low EFV concentrations with phenytoin. Monitor anticonvulsant and EFV levels. If possible, alternative anticonvulsant should be used.	
METHADONE	Levels: DLV unchanged; no data on methadone levels but potential for increased levels. Monitor for methadone toxicity; may require a dose reduction.	Levels: Methadone ↓ 60%. Opiate withdrawal common; increased methadone dose often necessary. Titrate methadone dose to effect.	Levels: NVP unchanged. Methadone ↓ significantly. Opiate withdrawal common when this combination is used; increased methadone dose often necessary. Titrate methadone dose to effect.
MISCELLANEOUS	May increase levels of dapsone, warfarin, and quinidine. Sildenafil: Potential for increased concentrations and adverse effects. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. Vardenafil: No data, but vardenafil AUC may be substantially increased.Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Tadalafil: No data, but concomitant administration will likely result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mg dose and do not exceed a single dose of 10 mg every 72 hours. Co-administration of fluoxetine increases DLV Cmin 50%.	Monitor warfarin when used concomitantly.	No data.

* These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

Table 21c. Drug Interactions Among Antiretrovirals and Other Drugs: NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Didanosine (ddI)**	**Stavudine (d4T)**	**Tenofovir (TDF)**	**Zidovudine (ZDV)**
Atazanavir (ATV)	Levels: Buffered ddI + ATV simultaneously: ↓ AUC of ATV 87%. Take ATV with food 2 hrs before or 1 hr after buffered ddI. Simultaneous EC ddI + ATV (with food): ↓ AUC of ddI 34%. ATV no change. Administer separately; ATV should be taken with food and ddI-EC on an empty stomach.	No data.	ATV 400 mg + TDF 300 mg - Levels: ATV AUC ↓ 25% and Cmin ↓ 40%. TDF AUC ↑ 24%. Avoid concomitant use without RTV. ATV + RTV 300/100 mg QD + TDF 300 mg QD - Levels: ATV AUC ↓ 25% and Cmin ↓23%; ATV Cmin higher with RTV than without . TDF AUC ↑ 30%; monitor for toxicities. Dose: ATV + RTV 300/100 mg QD co-administered with TDF 300 mg QD.	ZDV: No change in AUC but 30% ↓ in Cmin. Significance unknown.
Cidofovir, Valganciclovir	Buffered ddI + ganciclovir (GCV): ddI AUC ↑ 50%-111%; GCV AUC ↓ 21% when ddI administered 2 hours prior to oral GCV; no change in IV GCV concentrations. Appropriate doses for the combination of ddI and GCV have not been established.	No data.	Serum concentration of these drugs and/or tenofovir may be increased. Monitor for dose-related toxicities.	Ganciclovir + ZDV: No significant changes in levels for either drug. Potential increase in hematologic toxicities.
Didanosine	•	Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; should be avoided unless potential benefit far outweighs potential risks.	Levels: ddI EC AUC ↑ by 48-60%, Cmax ↑ by 48-64% For patients >60 kg, 250 mg/day of ddI EC is recommended; for patients <60 kg, 200 mg EC ddI is recommended; the ddI doses apply to patients with creatinine clearanace >60 mL/min. Monitor for ddI-associated toxicities.	No significant interactions.
Indinavir (IDV)	Buffered ddI and IDV simultaneously: Levels: ↓ AUC of IDV; take IDV 1 hr before or after buffered ddI. EC ddI can be taken together with IDV.	No significant PK interaction.	Levels: IDV Cmax ↑ 14%. Dose: Standard.	No significant PK interaction.
Lopinavir/ritonavir (LPV/r)	No data.	No data.	LPV/r 400/100 mg AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown; monitor for tenofovir toxicities.	No data.
Methadone	Levels: EC ddI unchanged. Buffered ddI AUC ↓ 63%; methadone unchanged. Dose: No change EC ddI. May consider buffered ddI dose increase or maintain standard.	Levels: d4T ↓ 27%; methadone unchanged. Dose: No dose adjustment.	No change in methadone or TDF levels.	ZDV AUC ↑ 43%. Monitor for ZDV-related adverse effects.
Ribavirin	Co-administration not recommended. Ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities.	No data.	Level: Ribavirin unchanged; no data on TDF level.	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible, or closely monitor virologic response.
Tipranavir/ ritonavir	Levels: EC ddI ↓ 10%.[a] TPV Cmin ↓ 34% with EC ddI.[a] Buffered ddI ↓ 3%-33%.[a] Dose: EC ddI and TPV/r should be separated by at least 2 hours.	No significant PK interaction.	TPV AUC and Cmin ↓ 9%-18% and 12%-21%, respectively[a]; clinical significance is unknown.	Levels: ZDV AUC and Cmax ↓ 31%-42% and 46%-51%, respectively.[a] Appropriate doses for the combination of ZDV and TPV/r have not been established.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200 mg BID.